EPIDEMIOLOGY

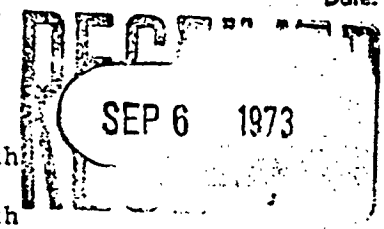
#941
Part I

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8985

Application for Research Grant
(Use extra pages as needed)

Date:



1. Principal Investigator (give title and degrees):
Henry T. Lynch, M.D., Professor and Chairman
Department of Preventive Medicine & Public Health
Hoda Guirgis, Ph.D., Assistant Professor
Department of Preventive Medicine & Public Health

2. Institution & address:

Creighton University School of Medicine
2500 California Street
Omaha, Nebraska 68178

3. Department(s) where research will be done or collaboration provided:

Department of Preventive Medicine and Public Health

4. Short title of study:

Hereditary Factors, Cigarette Smoking, and Cancer Incidence in 3,261 Families.

5. Proposed starting date: 9/1/73

6. Estimated time to complete: 2 years

7. Brief description of specific research aims:

a). To evaluate smoking histories in a population characterized by familial proneness to cancer or familial absence of cancer. This population represents the first example of ascertainment of family histories of cancer from a large number of normal probands.

b). To determine the status of heredity and its interaction with cigarette smoking history with objective evidence of cancer occurrences (all sites) in the several categories of cancer proneness versus cancer resistance, i.e., families with complete absence of cancer, families with one first degree relative with cancer, and families with two or more first degree relative with cancer.

c). Statistical analysis will be made in search for correlations with specific histologic varieties of cancer and to relate this issue to the family history of cancer in the presence or absence of cigarette smoking.

d). Diet, alcohol consumption, occupational exposures, and any cultural idiosyncrasies will be evaluated in context with their potential etiologic influences as contributory factors in carcinogenesis.

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8. Brief statement of working hypothesis:

We propose that an individual's genetic endowment is an important determinant in susceptibility to specific carcinogens. Since liability or proneness to a disorder is a function of interacting environmental and genetic factors, one would expect to find a variation in cancer-resistant and cancer-prone families with a change in either factor. If two families come from environments which are not strikingly different from each other, but show a variation in proneness to cancer one can assume that the major differentiating variable is the genetic factor. Thus, an individual's predisposition or resistance to a particular disease process depends upon that individual's genetic norm or range of reaction and the environmental factors interacting with his genotype.

Should this hypothesis prove to be correct, it would follow that cigarette smoking may pose an unusual health hazard to certain patients in a manner not unlike the current hypothesis suggesting an acceleration of the clinical course of emphysema in individuals who are cigarette smokers and who harbor genes for alpha$_1$ antitrypsin deficiency. Therefore, this hypothesis may in part explain the fact that the overwhelming majority of smokers do not contract lung cancer (or any other cancers). On the other hand, those cigarette smokers who do develop carcinoma of the lung and/or other cancers may represent a genetically susceptible population. Some of these patients would undoubtedly develop cancer spontaneously in the absence of cigarette smoking though they may have been subjected to other environmental carcinogens.

9. Details of experimental design and procedures (append extra pages as necessary)

Our population is unique in that it represents the first major effort in defining the frequency of cancer of all anatomic sites in a large number of families ascertained through evaluation of apparently healthy individuals. The initial studies were performed independently at two geographically distinct medical centers and were based upon 4,283 subjects from which over 5,000 families were generated. The statistical analysis showed virtually identical overall findings from these two populations (Tables 1-4 and Figures 1-4). The study group from which our samples will be derived will comprise 3,261 Nebraska families of which our investigators have established personal contact through our cancer screening activities of the probands. Thus, rapport has been well established, contributed to in part by the fact that a service, namely cancer screening was provided to all of these individuals. Finally, the activities of the research team with this group are current in that the screening activities have been conducted within the last two years.

The number of probands screened at the mobile cancer detection unit in eight locations is listed in Table 5. The geographic distribution of these locations in the state of Nebraska are shown in Figure 5. As described in Table 1, we find that 46.6 percent of the probands show no cancer history in their first degree relatives. We also find 29.3 percent had a first degree relative affected with cancer and 26.1 percent had 2 or more first degree relatives with a history of cancer.

In this study we will collect data on probands and their first degree relatives only, i.e., parents of probands, siblings of probands, and children of probands.

Random sampling and groups under study:

The method described by Goldstein (1964) will be adopted in this study. That is, each proband will be assigned a number; using the random tables we then begin filling the groups according to the sequences of numbers in the table.

Using this method the following groups will be selected:

(Group A) 200 probands having no history of cancer in first degree relatives selected from the 46.6% of total probands.

(Group B) 100 probands will be drawn from the pool of probands that had a history of one first degree relative affected with cancer selected from the 29.3% of all probands.

(Group C) 100 probands will be drawn from these probands that had 2 or more first degree relatives that had cancer selected from the 26.1%. The total number of probands will then be 400.

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Letters will be sent to each of the 400 probands explaining the nature of this study, and asking for their participation in it. A questionnaire will be included so that prior to an interview each proband will complete the following information:

1. Names and addresses of all first degree relatives.
2. Medical history authorization forms.
3. Additional medical history since the date of initial screening at the mobile unit.
4. Smoking and family history questionnaire to be completed by each first degree relatives following interviews with probands.

In each interview, details of smoking history including the specific type of smoking (cigarettes, cigars, pipe, chewing tobacco) including onset of smoking, duration, continuous versus discontinuous pattern, and so on, will be obtained on the specific patient being interviewed as well as the knowledge of smoking habit patterns in his or her first degree relatives. Thus, through interviewing a minimum of three patients from each family (the patient seen in the clinic and two or more first degree relatives), in addition to material from questionnaires in all first degree relatives we would have available to us sufficient information to cross check and thereby validate our historical information.

The effects of diet or tumor formation particularly in the gastrointestinal tract has resulted in intensive etiologic speculation in the world literature in recent years, since variations in tumor incidence among different nationality groups could be explained by dietary and perhaps other as yet unknown environmental effects. As a result of increasing affluence, the American diet is noted both for its high meat content and the use of convenience foods--most of which are of low bulk and highly refined. Of increasing concern has been the use of herbicides and pesticides in efforts to increase crop production; these may have possible effects on humans. Although an extensive dietary history might contain too many variables and may be too difficult to elicit, major differences in food intake may become evident by determining the patient's individual preference from food lists, as well as a rough estimate of the amount consumed. For all practical purposes, we propose to simplify our dietary history by dividing foods into four groups: 1) a meat-poultry-egg group; 2) cheese and dairy products; 3) bread and cereals; 4) fruit and vegetables. In the first part of the history, an effort will be made to determine the patient's food preferences; in the second part, an attempt will be made to evaluate size of servings, and the number of meals consumed per day. Since studies on food consumption have been published by the Department of Agriculture yearly, extending back to 1848, an attempt will be made to compare our patient's food intake with those compiled by the Department of Agriculture, and to investigate any major variation which might be found.

Following completion of the questionnaire and interview material on each family, the data will be reviewed by our Genetic Study Group Research Team, it will be analyzed, and a pedigree will be constructed. As with previous studies of this nature by our group, the amount of data obtained will require an extensive filing system, with appropriate clerical assistance. The use of a computer is also projected for the statistical evaluation of the data. These facilities are available to us.

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There are several possible results which might be achieved from this study as follows:

1. There may be no difference in the smoking history in the population identified as being cancer free so far as probands and first degree

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relatives are concerned versus that population which admits to one or more first degree relatives with cancer. Such a finding would suggest, but of course by no means confirm, that at least for the smoking issue there does not appear to be an important etiologic effect.

2. We may find a significant relationship between smoking and the presence of cancer in the population prone to cancer versus the population free of cancer. Again, such a conclusion might suggest an etiologic role for smoking, but still this would merely indicate an association but in no way would it indict this as a cause-effect relationship. However, the significance of the association would be more strong if the cancers found in the population prone to cancer and showing an excess of smoking, were carcinomas of the lung, oral cavity and pharynx, esophagus, kidney, or urinary bladder, malignant neoplasms which heretofore have been shown to have a greater or lesser degree of statistical association with smoking history. However, even here we would not be certain of this association, since it could well imply that certain personality characteristics, possibly on a familial basis, may be associated with both cigarette smoking and a predisposition to these and other malignant neoplasms.

3. We may find an excess of cigarette smoking habit amongst the patients and their first degree relatives who have been shown to have a negative family history of cancer when compared to the cancer prone group. Such a finding as this might suggest that, at least in this rather large and generally heterogeneous population, . . cigarette smoking does not appear to play an important role in cancer etiology in this population.

4. Finally, we may find no statistically significant difference in smoking histories between the cancer prone population and the cancer free population. Such a finding as this would suggest that so far as the alleged carcinogenic effect of cigarette smoking is concerned, that it does not appear to play a significant etiologic role in cancer in a population designated as cancer prone versus a population designated as cancer free. This would tend to add strength to the hypothesis that familial factors and/or genetic factors play a more prominent role in carcinogenesis when at least one possible carcinogenic agent, namely cigarette smoking, is critically analyzed. However, we must also be cautious about these and other observations mentioned above because myriad other exogenous factors, i.e., industrial exposures, variations in trace metals in water supply, dietary differences, solar radiation exposure, other agents under study, including asbestos, as well as agents heretofore unidentified . . . so far as carcinogenesity is concerned may be of crucial importance; and therefore the role of host factors will never by fully delineated in man until all possible exogenous carcinogenic agents are critically analyzed in each patient. Of course, such a complete study as this would be impossible to perform in man, particularly since man is a participant in an extremely competitive, variable, and markedly mobile society. On the other hand, a study of the type we are proposing could provide us with further insight into the possible relationship between an agent which has been claimed by many to be an extremely important cause of cancer, namely cigarette smoking, and the relative relationship to host factors in cancer etiology.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

A). The office facilities of the Department of Preventive Medicine.

B). We have computer facilities with a 310 computer, available to us under the direction of Rev. Edward Sharp.

C). Olivetti calculator 270 and a desk computer.

D). We have a Winnebago (27 foot) mobile camper equipped with facilities for interviews and for examinations when indicated. The interviewing area affords for complete privacy.

11. Additional facilities required:

None are required

12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available):

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14. First year budget:

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
Medical social worker or Registered nurse with MPH	100%	$13,000
Biostatistician	25%	4,000
		17,000
Technical		
Secretary	50%	3,000
	Total	20,000
	Fringe	1,4000
	Sub-Total for A	21,400
B. Consumable supplies (by major categories)		
Stationery, stamps, etc.		1,000
Computer supplies		1,000
	Sub-Total for B	2,000
C. Other expenses (itemize)		
Travel for interview		3,000
	Sub-Total for C	3,000
	Running Total of A + B + C	26,400
D. Permanent equipment (itemize)		
	Sub-Total for D	
E. Indirect costs (15% of A+B+C)	E	3,960
	Total request	30,360

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	22,684	2,000	3,000		4,153	31,837
Year 3						

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16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Hereditary Progressive A-V Conduction Defect	HEW 1 R01 HL 15903-01	$35,000	9/1/73 - 8/31/74
Breast Cancer Family Resources	HEW-N01-CB-33901	95,120	7/1/73 - 6/1/74
Genetics of Cardiac Conduction Defects: Family Studies	Nebraska Heart Association	7,158	7/1/73 - 6/31/74
Order of Eagles		10,000	

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Prospective Genetic Studies of Colon and Lung Cancer: Host Environment Considerations	Research Council at Omaha Veterans Administration Hospital	$14,200	9/1/73 - 8/1/75
Additional Clinical Centers for the Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease	RFP-NHLI-74-1	289,101	9/1/74 - 8/1/75
Carcinoembryonic Antigen in Two Cancer Prone Families	NIH - Ca 15635-01	100,503	9/1/73 - 8/31/76

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Check payable to

Mailing address for checks

Principal investigator

Typed Name

Signature [signature] Date 9/5/73

Telephone Area Code Number Extension

Responsible officer of institution

Typed Name Frank Evans

Title Asst. to the Dean for Financial Affairs

Signature [signature] Date 9/5/73

Telephone Area Code Number Extension

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APPENDIX

Epidemiologic Background in Support of Hypothesis

Cancer is not uniformly distributed in the population. There are marked variations in cancer incidence at diffenent anatomic sites, in different populations, and in different areas of the world. Numerous etiologic differences account for such variations in cancer incidence, including differences in genotypes,[1] environmental exposures, habit patterns, occupations, socioeconomic status, and educational factors. A comprehensive exploration of cancer etiology involves integrated consideration of all potentially mitigating factors, not only individually, but also collectively as they interact with each other.[1-16]

As we studied families with significantly increased incidences of cancer, compared to the general population, we observed significant paucities in occurrences of the cancers in certain branches of these families and in a number of other families, some of which included the kin of spouses of patients in high-incidence families. We concluded that some kindreds may be characterized by unusual resistance or decreased susceptibility to cancer, just as other kindreds may be characterized by unusual cancer-proneness. This observation is not surprising because significant differences in cancer resistance have been well established in inbred strains of a variety of animals.[17-19] Recent studies in tumor immunology have revealed a crucial relationship between an animal's immune defense system and its response to carcinogens as well as to transplanted cancer cells.[20,21] Stephenson et al.[22] have discussed spontaneous regression of tumors in humans in relation to tolerance and/or resistance to malignancy.

We have made extensive observations of two extended families, or kindreds, which show strikingly increased incidences of cancers[5,6,23] and have compared these findings with those from two other families studied in a similar manner but in whom the incidence of cancer is far less than that found in the general population.[24] Thus, we have identified families characterized by unusual proneness

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to cancer (50 percent in some branches) and others which appear to be resistant to cancer (frequency of cancer of 1 percent or less). We believe that genotypic factors are important in determining these differences which have been observed consistently through multiple generations.

Cancer Genetics and Epidemiology

Discussions of the etiology of "cancer", which is a generic term, are largely meaningless. If cancer is to be delineated further, through acquisition of information relevant to the circumstances surrounding onset, then it will be necessary to design studies of specific histologic varieties of cancer. Thus, for example, adenocarcinoma of the colon may occur as a result of excessive irradiation to the abdomen in treatment for another disease such as endometrial carcinoma or abdominal lymphoma; it may occur spontaneously due to unknown etiology without any known mitigating circumstances; it may occur in context with longstanding active ulcerative colitis; it may result from familial polyposis coli, a condition transmitted by an autosomal dominant gene; or it may result from any of several other inherited precancerous disorders.[2] Malignant neoplasms such as adenocarcinoma of the colon may also congregate in certain families in whom the genetic mechanism may be unclear or may be ascribed to multifactorial inheritance.

Multifactorial genetic transmission has been considered as possibly being etiologic in several diseases with variable age of onset, with incidence increasing with age, and with increased empirical risks to relatives of probands. Multiple genetic factors may be involved in each of several histologic varieties of cancer which tend to congregate on a familial basis. Breast cancer, which shows familial tendencies but does not show simple Mendelian patterns of genetic transmission, may fit such an etiologic classification.[14]

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Cancer resistance may be determined on a multifactorial basis. Therefore, it is reasonable to ask the question, "Are families which show a remarkable freedom from cancer receiving this protection on a basis of multiple-gene-transmitted constitutional characters?" Falconer[24] suggests that, when considering diseases which may fall into the category of multifactorial inheritance, one should consider together both genetic and environmental factors which make a particular individual more or less likely to develop a disease such as cancer or diabetes mellitus, and that these should be combined into a single measure which he refers to as the individual's "liability". He reasons that the liabilities of individuals in a population form continuous variables and that the apparent discontinuities between "affected" and "normal" arise from "threshold" differences at some levels of the liabilities. Thus, individuals with liabilities above the threshold are affected, and individuals with liabilities below the threshold are not. The liability of any one individual cannot be measured with precision. On the other hand, however, mean liability may be evaluated for a population or group from the incidence of the disease in that population or group. Thus, liability can in principle be expressed in units on a scale that renders its distribution normal (i.e., fitting a Gaussian or normal curve), and measurements of the mean liability then become the standard deviations on the scale.

According to Falconer[24] "The analysis provides an estimate of the correlation between relatives in respect to liability, and this leads, with certain assumptions, to an estimate of the heritability of liability in the population. The heritability is the proportion of the variance of liability that is ascribable to additive genetic variance. This is the nearest to which one may approach, with human data, the degree of genetic determination of liability. The data required for the analysis are the incidence of the disease in the

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population and the incidence in relatives of affected propositi drawn from the population".

The liability or proneness to a disorder is a function of interacting environmental and genetic factors. These factors operate in differing orders of magnitude depending upon the individual's specific genetic and environmental circumstances. Thus, when environmental factors are more significant, the relative effects of hereditary factors will be less significant. Since families that are cancer-resistant or cancer-prone may be associated with environments which are not strikingly different from each other, a major differentiating variable may be genetic factors.

A heritability determination is an estimate of the proportion of the total phenotypic variance (i.e., individual differences) that can be attributed to genetic variation in a single generation of some particular population under one set of environmental conditions. The heritability of cancer may be defined as the extent to which variation in individual risk of acquiring cancer is due to genetic differences. A disease will show a greater-than-zero heritability if two or more segregating genetic alleles, which manifest different effects upon predisposition and resistance to the disease, occur on at least one chromosomal locus. Such a trait may show different heritabilities in different populations which are characterized by genotypic and/or environmental differences, because the manifestations of any particular gene depend upon interactions between that gene and the overall genotype as well as with nongenetic or environmental variables. An individual's predisposition or resistance to a particular disease process depends upon that individual's genetic norm or range of reaction and the environmental factors interacting with his genotype. A genetic factor may be manifested only by appropriate genotype-environment combinations. A gene's harmfulness or usefulness is determined by the bearer's environment. Thus, the genetic epidemiologist functions as an

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ecologist seeking significant correlations between a disorder and one or another variable from the great array of environmental influences. One's success in such research is related to the uniqueness of the variable and the directness of its effect, to the frequency of the disorder, and to the ease of diagnosing the disorder.

The cancer epidemiologist must constantly scrutinize all possible hereditary and environmental factors which could be of etiologic importance in the development of cancer. Unfortunately, many studies have concerned themselves only with single carcinogenic factors. Very few attempts have been made to relate nongenetic factors to host factors, e.g., cigarette smoking and family history,[25] solar radiation and cancer induction in patients with xeroderma pigmentosum,[3,4] etc. Few studies have been specifically concerned with cancer resistance in humans.[20,21]

Rationale

Our group has developed new data pertaining to the distribution of cancer in a relatively sizable population (3,261) of allegedly well patients who come to a mobile cancer detection unit for purposes of cancer screening. This was an unselected population, though it may well harbor a slight bias in that motivational factors may have been important in initiating the visit to the unit. However, we believe that the findings that 47% of the patients coming to the unit showed a negative family history of cancer in first degree relatives, a point confirmed with practically identical statistical results by a colleague, Michael Brennan, M.D. and associates at the Michigan Cancer Foundation in Detroit. We believe that these patients and their families harbor an important potential for studies of potentially significant carcinogenic agents in context with genotypic factors which could be important in determining cancer frequency and distribution in the respective families. Thus, it would seem important

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that carcinogenic agents be critically analyzed in context with host factors. Studies at the infra-human level have shown repeatedly that a relationship exists between genetic factors and cancer susceptibility, i.e., identified through selective inbreeding studies in a variety of animal populations producing highly inbred strains, and that these host factors are important in controlling the predisposition to cancer; and moreover, they also predispose such animals to the effects of certain carcinogens, and therefore potentiate oncogenicity. We offer a similar rationale and hypothesis for cancer occurrence in man, namely host factors may be important in determining differential oncogenicity to selected carcinogenic agents.

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13. Publications

1. Lynch, H.T.: Hereditary Factors in Carcinoma. In: Recent Results in Cancer Research. Springer-Verlag, New York, 1967.

2. Lynch, H.T. and Krush, A.J.: Heredity and Adenocarcinoma of the Colon. Gastroenterology 53:517-527, 1967.

3. Lynch, H.T., Anderson, D.E., Krush, A.J., and Mukerjee, D.: Cancer, Heredity, and Genetic Counseling: Xeroderma Pigmentosum. Cancer 20: 1796-1801, 1967.

4. Lynch, H.T., Anderson, D.E., Smith, J.L. Jr., Howell, J.B., and Krush, A.J.: Xeroderma Pigmentosum, Malignant Melanoma, and Congenital Ichthyosis: A Family Study. Arch. Dermatol. 96:625-635, 1967.

5. Lynch, H.T. and Krush, A.J.: Cancer Family "G" Revisited: 1895-1970. Cancer 27:1505-1511, 1971.

6. Lynch, H.T., Shaw, M.M., Magnuson, C.W. and Krush, A.J.: Hereditary Factors in Cancer: Study of Two Large Midwestern Kindreds. Arch. Intern. Med. 117: 206-212, 1966.

7. Gianferrari, L., Morganti, G.: Ricerche Sulla Familiarità Neoplastica. Acta Genet. Med. Gemellol. 6:217-224, 1957.

8. Beolchini, P.E., Cresseri, A., Gianferrari, L., Malcovati, P., and Morganti, G.: Ricerche Genetiche Sulle Neoplasie dell'Utero (Parte I). Acta Genet. Med. Gemellol. 5:462-468, 1956.

9. Beolchini, P.E., Cresseri, A., Gianferrari, L., Malcovati, P., and Morganti, G.: Ricerche Genetiche Sulle Neoplasie dell'Utero (Parte II). Acta Genet. Med. Gemellol. 6:59-84, 1957.

10. Beolchini, P.E., Cresseri, A., Gianferrari, L., Malcovati, P. and Morganti, G.: Ricerche Genetiche Sulle Neoplasie dell'Utero (Parte III). Acta Genet. Med. Gemellol. 7:47-90, 1958.

11. Lynch, H.T., Larsen, A.L., Magnuson, C.W., and Krush, A.J.: Prostate Carcinoma and Multiple Primary Malignancies: Study of a Family and 109 Consecutive Prostate Cancer Patients. Cancer 19:1891-1897, 1966.

12. Lynch, H.T., Krush, A.J., Larsen, A.L., and Magnuson, C.W.: Endometrial Carcinoma: Multiple Primary Malignancies, Constitutional Factors, and Heredity. Amer. J. Med. Sci. 252:381-390, 1966.

13. Lynch, H.T., Guirgis, H., Swartz, M., Lynch, J., Krush, A.J., and Kaplan, A.R.: Genetics and Colon Cancer. Arch. Surg. 106:669-675, 1973.

14. Lynch, H.T., Krush, A.J., Lemon, H.M., Kaplan, A.R., Condit, P.T., and Bottomley, R.H.: Tumor Variation in Families with Breast Cancer. J.A.M.A. 222:1631-1635, 1972.

15. Lynch, H.T. and Krush, A.J.: Carcinoma of the Breast and Ovary in Three Families. Surg. Gynec. Obstet. 133:644-648, 1971.

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16. Lynch, H.T., Krush, A.J., Harlan, W.L. and Sharp, E.A.: Association of Breast Cancer, Soft Tissue Sarcoma, Leukemia, and Brain Tumors in Breast Cancer Families. Amer. Surg. 39:199-206, 1973.

17. Jacobs, B.B.: Growth of Tumors in Allogenic Hosts After Organ Culture Explanation. II. Tumor-host Interactions. J. Natl. Cancer Inst. 42: 537-543, 1969.

18. Stern, K., and Goldfeder, A.: Radiation Studies on Mice of an Inbred Tumor-Resistant Strain. VI. Immune Responses to Heterologous Red Cells of Non-Irradiated and Radiated Mice. Int. Arch. Allergy, Appl. Immunol. 35:504-513, 1969.

19. Waters, N.F., Burmester, B.R.: Mode of Inheritance of Resistance of Rous Sarcoma Virus in Chickens. J. Natl. Cancer Inst. 27:655-661, 1961.

20. Moore, G.E.: Cancer Immunity: Fact or Fiction? Tex. Med. 64:54-59, 1968.

21. Hellström, I., Hellström, K.E., Pierce, G.E., Yang, J.P.S.: Cellular and Humoral Immunity to Different Types of Human Neoplasms. Nature (Lond.) 220: 1352-1354, 1968.

22. Stephenson, H.E., Delmez, J.A., Renden, D.E., Kimpton, R.S., Todd, P.G., Charron, T.L., and Lindberg, D.A.B.: Host Immunity and Spontaneous Regression of Cancer Evaluated by Computerized Data Reduction Study. Surg. Gynecol. Obstet. 133:649-655, 1971.

23. Hauser, I.J., Weller, C.V.: A Further Report on the Cancer Family of Warthin. Am. J. Cancer 27:434-449, 1936.

24. Falconer, D.S.: The Inheritance with Liability to Diseases with Variable Age of Onset, with Particular Reference to Diabetes Mellitus. Ann. Hum. Genet. 31:1-20, 1967.

25. Tokuhata, G.K.: Familial Factors in Human Lung Cancer and Smoking. Am. J. Public Health 54:24-32, 1961.

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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

TABLE 1

Distribution of Participants in Omaha and Detroit to the Number of Cancers in the Family

Category	Group I Participants Number	Group I Participants Percent	Group II Participants Number	Group II Participants Percent
No History of Cancer	1520	46.6	470	46.6
History of a Single Cancer	1082	33.2	296	29.3
History of Multiple Cancers	659	20.2	243	24.1
Total	3261	100.0	1009	100.0

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TABLE 2

DISTRIBUTION OF BREAST AND OTHER CANCERS IN GRANDMOTHERS, MOTHERS AND AUNTS OF PARTICIPANTS UNDER 45 YEARS

Group No.	Relation to Participant	No. of Breast Cancers	No. of Other Cancers	Total Cancers	% of Breast Cancer
		Number	Number	Number	Percent
Group I	Grandmothers	37	178	215	17.2
	Mothers	45	90	135	33.3
	Aunts	58	154	212	27.4
Group II	Grandmothers	66	178	244	27.0
	Mothers	44	52	96	45.8
	Aunts	74	135	209	35.4

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TABLE 3

DISTRIBUTION OF BREAST AND OTHER CANCERS

IN FEMALE RELATIVES OF PARTICIPANTS

45 YEARS OF AGE AND OVER

	Breast Cancer	Other Cancer	Total Cancer	% of Breast Cancer
Mothers	80	377	457	17.5
Sisters	100	279	379	26.4
Female probands	42	88	130	32.3
Proband's daughters	6	44	50	12.0

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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

TABLE 4

THE OCCURRENCE OF BREAST AND OTHER CANCERS IN LINEAGES OF PARTICIPANTS

	Group I		Group II	
	No. of Lineages Involved 1244		No. of Lineages Involved 2044	
	Number	Percent	Number	Percent
1 breast cancer and no other cancer	59	4.7	84	4.1
1 breast cancer + 1 other cancer	35	2.8	58	2.8
1 breast cancer + 2 other cancers	12	1.0	5	0.2
1 breast cancer + 3 other cancers	2	0.2	3	0.1
2 breast cancers and no other cancers	7	0.6	6	0.3
2 breast cancers + 1 other cancer	1	0.1	7	0.3
2 breast cancers + 2 other cancers	2	0.2	3	0.1

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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

TABLE 5

Total Number Screened in Each Location

Town	Total	Male	Female
Macy	280	78	202
Winnebago	197	66	131
Lynch	670	262	408
Bassett	466	131	335
South Sioux City	279	84	195
Tekamah	680	196	484
Holdrege	241	62	179
Omaha	220	66	154

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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

Figure 1

The history of cancer of all sites in families studied in Groups I and II

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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

Figure 2

The distribution of breast and other cancers in Grandmothers, mothers and aunts of participants under the age of 45 years in Groups I and II

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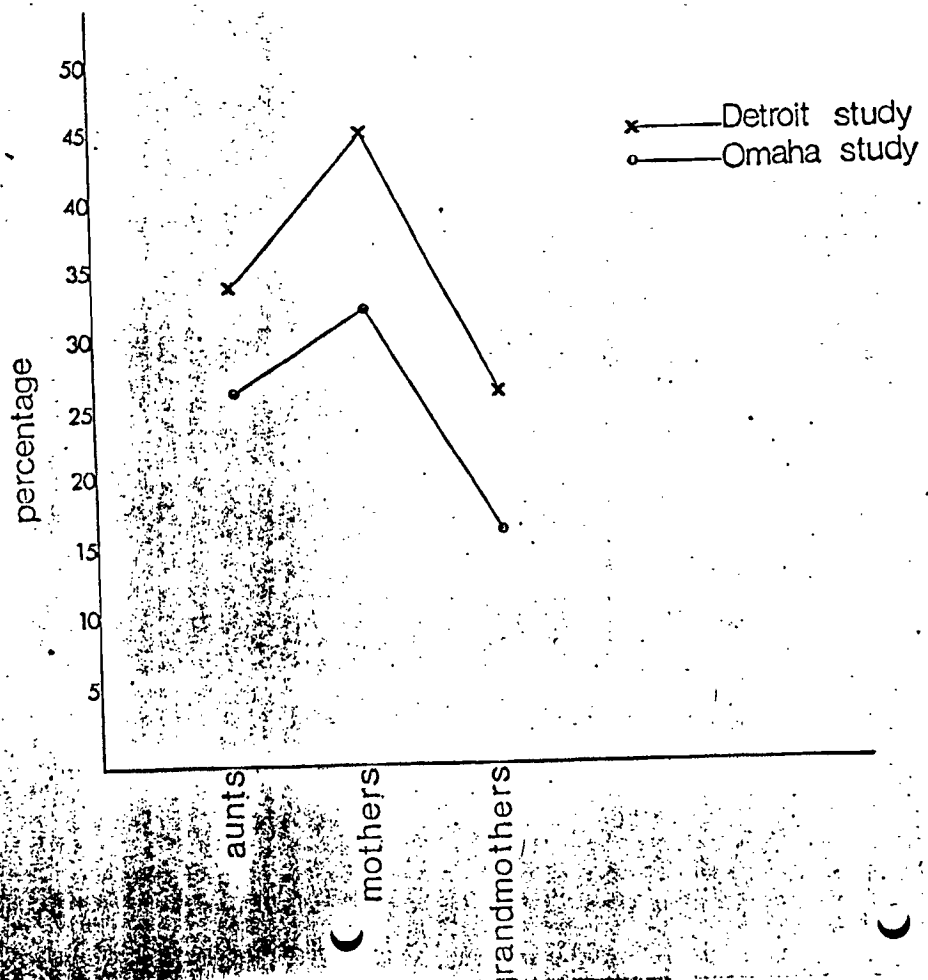
Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

Distribution of Breast Cancers



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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

Figure 3

Death rates per 100,000 of breast cancer in United States from the years 1900-1970

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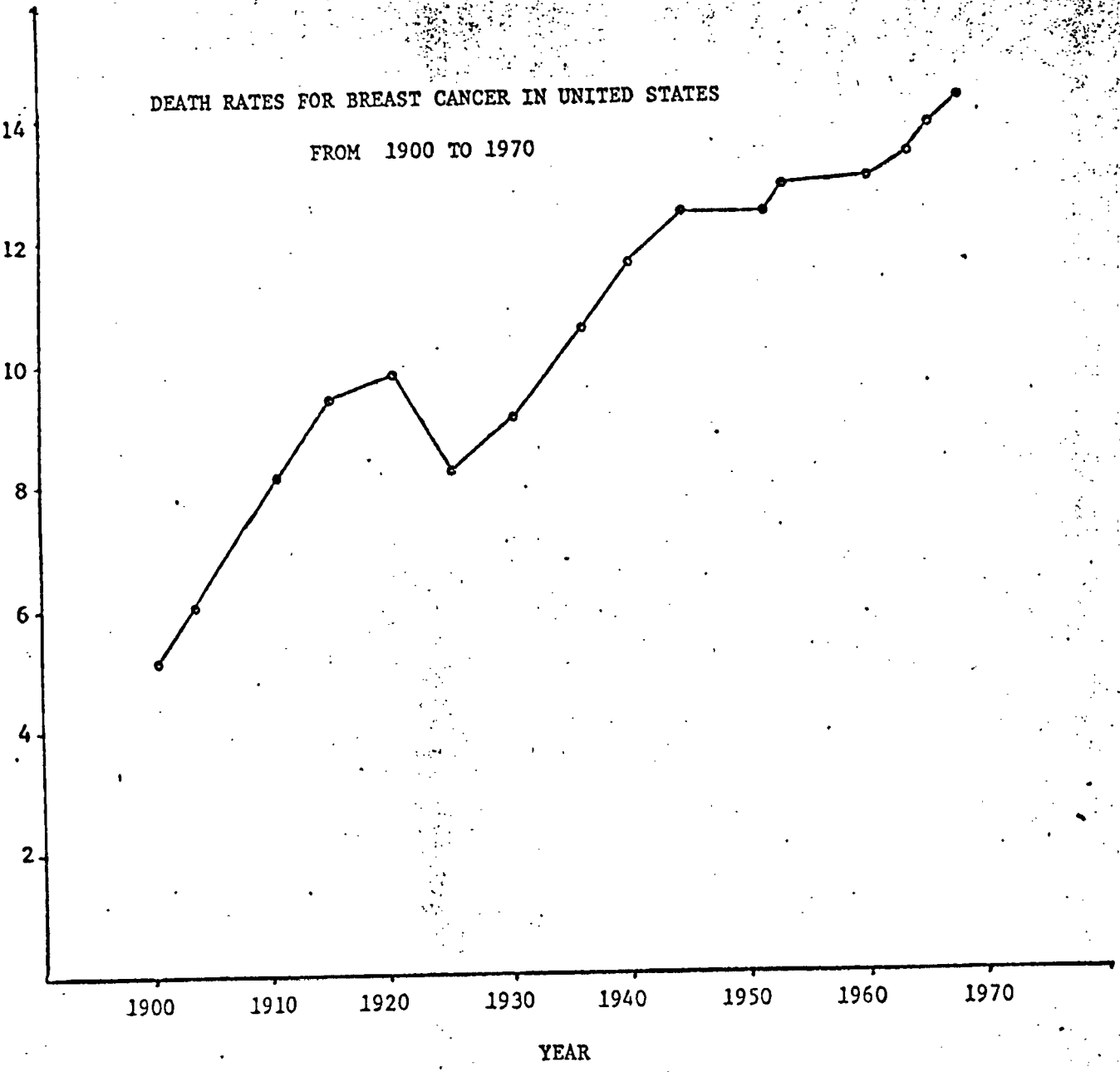
Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000



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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

Figure 4

A cross comparison of associations of carcinoma of the Breast, Stomach, Colon, Endometrium, and Ovary of families studied

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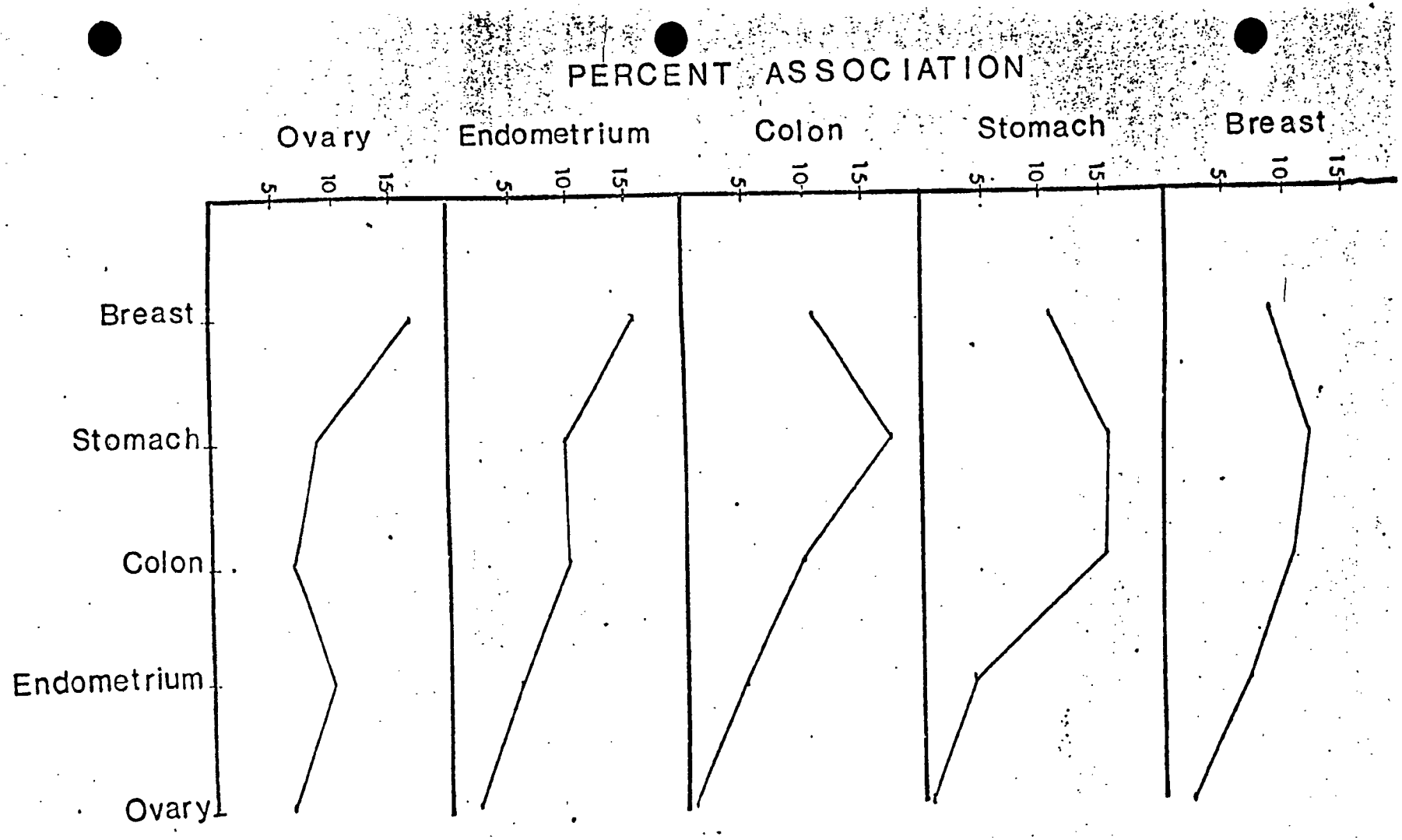
Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000



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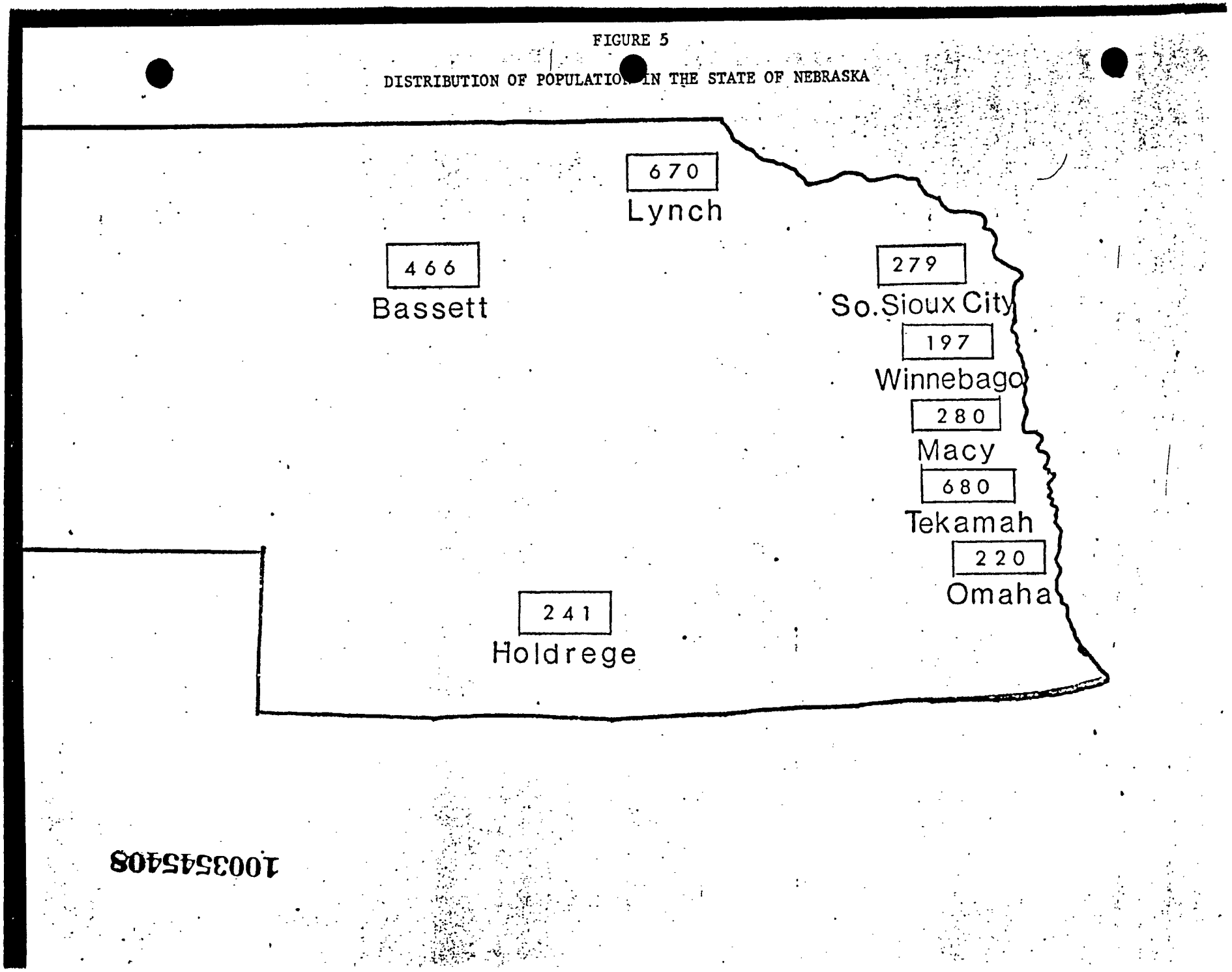
Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

FIGURE 5

DISTRIBUTION OF POPULATION IN THE STATE OF NEBRASKA



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Source: https://www.industrydocuments.ucsf.edu/docs/qmdm0000

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SECTION II – PRIVILEGED COMMUNICATION

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Henry T. Lynch	Principal Investigator	R

PLACE OF BIRTH (City, State, Country)	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)	SEX
REDACTED		☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
University of Oklahoma, Norman, Oklahoma	B.S.	R	Psychology
Denver University, Denver, Colorado	M.A.	R	Psychology
University Texas, Med. Branch, Galveston	M.D.	R	Medicine

HONORS Psy Chi, Honorary Society in Psychology, 1950. Society of Sigma Xi, 1959. Billings Silver Medal for Exhibit, "Heredity and Carcinoma: A Study of Cancer Families" (Presented to A.M.A., Chicago, June, 1966.

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Cancer and Medical Genetics	Principal Investigator

RESEARCH SUPPORT *(See instructions)*

1. Received NIH Training Grant: "Morbidity and Mortality from Hematopoietic and Solid Malignant Tumors and Their Possible Relationship to Dermographic and Ecologic Factors in a Community." #5A07 AH 00210-05 3/1/73-2/28/74 1972 - $5840 Total for 5 years= $29,200, Percent of effort = 10%.
2. Regional Med. Program (NIH) for Mobile Cancer Screening Unit, 1972-1973, $459,950 Percent of Effort = 10%.
3. Hereditary Factors in Adenocarcinoma of Colon--approved by, but not funded by Omaha VA Hospital (Supported by Damon Runyon Memorial Ca. Fund, 1969-1970. Percent of Effort = 10%
4. Biological Studies of the Ca. Family Syndrome, NIH approved, waiting for funding, 4/1973.

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

1967 to Present: Professor and Chairman, Department of Preventive Medicine and Public Health and Assistant Professor of Medicine, Creighton University School of Medicine, Omaha, Nebraska; 1966-1967: Assistant Professor of Biology, Assistant Internist, Department of Medicine (part-time), the University of Texas, M.D. Anderson Hospital and Tumor Institute, Houston, Texas; 1964-1966: Instructor, Internal Medicine; Senior Cancer Trainee, U.S.P.H.S., in Cancer and Allied Disease, Omaha, Nebraska; 1962-1965: Medical genetics consultant and lecturer, Department of Orthodontics, Lincoln, Nebraska; 1962-1964: Lecturer in Human Genetics, University of Nebraska College of Medicine, Omaha, Nebraska.

REPRESENTATIVE PUBLICATIONS

1. Lynch, H.T., Shaw, M.W., Magnuson, C.W., Larsen, A.L., and Krush, A.J.: Hereditary Factors in Cancer: Study of Two Large Midwestern Kindreds, Arch. Intern. Med. 117:206-212, 1966.

2. Lynch, H.T., Lemon, H.J., and Krush, A.J.: A Note on "Cancer-Susceptible" and "Cancer-Resistant" Genotypes: Implications for Cancer Detection and Research, Nebraska Med. J. 51:209-211, 1966.

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2 Lynch

REPRESENTATIVE PUBLICATIONS (Con't.)

3. Lynch, H.T., Anderson, D.E., Krush, A.J., and Larsen, A.L.: Heredity and Carcinoma, Ann. N. Y. Acad. Sci. 115:793-800, (December) 1968.

4. Lynch, H.T., Krush, A.J., and Larsen, A.L.: Heredity and Multiple Primary Malignant Neoplasms: Six Cancer Families, Amer. J. Med. Sci. 254: 322-329, (September) 1967.

5. Lynch, H.T., and Krush, A.J.: Heredity and Adenocarcinoma of the Colon, Gastroenterology 53:517-526, (October) 1967.

6. Lynch, H.T., and Krush, A.J.: The Cancer Family Syndrome and Cancer Control, Surg. Gynec. Obstet. 132:247-250, 1971.

7. Lynch, H.T., Harlan, W., Swartz, M.J., Marley, J., Becker, W., Lynch, J.F., Kraft, C.A., and Krush, A.J.: Multiphasic Mobile Cancer Screening: A Positive Approach to Early Cancer Detection and Control, Cancer 30: 774-781, 1972.

8. Lynch, H.T., Swartz, M.J., Lynch, J.S., and Krush, A.J.: A Family Study of Adenocarcinoma of the Colon and Multiple Primary Cancer, Surg. Gynec. Obstet. 134:781-786, 1972.

9. Lynch, H.T., Krush, A.J., and Guirgis, H.: Genetic Factors in Families with Combined Gastrointestinal and Breast Cancer, Amer. J. Gastroent. 59: 31-40, 1973.

10. Lynch, H.T., and Krush, A.J.: Differential Diagnosis of the Cancer Family Syndrome, Surg. Gynec. Obstet, 136:221-224, 1973.

11. Lynch, H.T., Guirgis, H.A., Swartz, M.W., Lynch, J.S., Krush, A.J., and Kaplan, A.R.: Genetics of Colon Cancer, Arch. Surg., In Press.

12. Lynch, H.T., Krush, A.J., and Kaplan, A.R.: Cancer Frequency Variations Among and Within Families, Acta Genet. Med. Gemellol. 21:53-65, 1972.

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